REMARKS/ARGUMENTS

Claims 4-16 are canceled.

Claims 17-18 are new.

Support for each new and amended claim is found throughout the specification and at the originally filed claims. The specification has been amended to change all instances of "SEQ ID No:" to "SEQ ID NO:".

Upon entry of the amendment, Claims 1-3 and 17-18 will be active.

No new matter is believed to have been added.

At the outset, Applicants respectfully traverse the Office's assignment of a filing date of November 28, 2003, for this application. Applicants note the Application is a continuation application of US Application No. 10/333,338, abandoned on December 10, 2003. The present application was filed on November 28, 2003, and this properly claims priority to US Application No. 10/333,338. US 10/333,338, in turn claims priority to International Application PCT/FR01/02371, filed on July 20, 2001. As the national stage entry date of US Application No. 10/333,338, was within the 30 months after the filing date of International Application No. PCT/FR01/02371, priority is properly claimed to International Application No. PCT/FR01/02371. Finally, as PCT/FR01/02371, was filed within one year of French Application No. 00/09600, (filing date of July 21, 2000), and French Application No. 00/12524 (filing date of October 2, 2000), an unbroken chain of continuity exists and the priority claim to both French Applications is therefore proper. Accordingly, Applicants request that the claim for priority under 35 U.S.C. 119(a)-(d) be honored.

The objection to the specification is believed to be obviated by the amendments to the specification. Applicants note the Office appears to be referencing the originally filed

specification, and that a substitute specification was filed on December 16, 2004. All specification amendments are based on the substitute specification page numbering.

The 35 U.S.C. 112, first paragraph, enablement rejection of Claims 1-3 and 5 is respectfully traversed. The rejection of Claim 5 is obviated by the cancellation of Claim 5. Claim 1 has been amended to require only microorganisms of a bacterial flora having an rpoBC operon in common, and require that the amplified region is the non coding intergenic region between rpoB and rpoC genes. Applicants submit that these amendments, and the additional amendments to Claims 1-3, render Claims 1-3 definite, especially regarding flora, amplification primers, and detection.

Flora:

Applicants submit these amendments render Claim 1, and the claims depending therefrom, definite, because a person wishing to employ the claimed method need only know the desired detection element, and it is not necessary to have exhaustive knowledge of the constituents of the Claim 1 flora.

Further, the "Online Textbook of Bacteriology, cited by the Office clearly describes that the main potential constituents of various floras are well-known to those skilled in the art.

Additionally, Applicants have submitted, along with this paper, a document entitled "Normal Flora." This document corresponds to chapter 6 of "Medical microbiology", edited by Samuel Baron, M.D., which is available at: http://gsbs.utmb.edu/microbook/ch006.htm. This document further supports that the main potential constituents of various floras are well-know.

Thus, the present inventive method may be performed for any bacterial flora, based on the general knowledge of those skilled in the art.

Amplification Primers

Further, amplification primers (Claim 3) are provided in the specification. The amplification primers are situated in coding regions of the genes of rpoB (SEQ ID NO:'s 1-8, 12-53, 56 and 58) and rpoC (SEQ ID NO:'s 9-11, 16-31, 54, and 59-61), are associated with conserved regions of the genes rpoB and rpoC and were designed taking into account genetic code degeneracy (Please see pages 9-10 of the specification).

In addition, the design of these primers is based on a sequence alignment of more then 50 microorganism species, thus showing the broad applicability of these primers (Please see page 20, lines 1-5 of the specification).

In particular, experimental results clearly show that primers represented by SEQ ID NO:'s 53 and 53 (Claim 17) allow for broad amplification of IGR (intergenic region) sequences from a wide range of species (Please see page 21, lines 11-18).

Identification:

The identification is performed by comparing the amplified IGR sequences to IGR sequences of known microorganisms. The specification provides IGR sequences of 76 different bacterial strains (SEQ ID NO:'s 63-138) thus allowing a person of ordinary skill in the art to broadly identify various microorganisms.

In addition, a person of ordinary skill in the art looking to determine the presence or absence of a particular microorganism in a given flora could easily, and without undue experimentation, sequence the IGR sequence of the particular microorganism utilizing the primers provided and then perform the method according to the invention to obtain the particular microorganism's identification.

Further, Applicants submit that sequencing of the IGR sequence of a limited number of microorganisms is routine for any person of ordinary skill in the art.

Accordingly, because the present method is enabled for flora, primers, and detection, Applicants submit the claim amendments and the disclosure of the specification render the claims definite. Withdrawal of the rejection is respectfully requested.

The indefiniteness rejection of Claims 1-3 and 5 is respectfully traversed. The rejection of Claim 5 is obviated by cancellation of this claim. Applicants respectfully submit that the amendments to Claims 1 – 3 render the claims definite. For example, proper antecedent basis is present in the claims, and gerunded steps have been provided in Claim 1. Withdrawal of the rejection is requested.

Applicants respectfully traverse the anticipation rejection of Claims 1-3 and 5 as being anticipated by Goh. The cancellation of Claim 5 obviates the rejection of this claim. The present claims are distinguished from Goh because in Goh, the amplified sequence is a coding sequence of gene HSP60, whereas present Claim 1 recites amplification of a non-coding intergenic sequence between genes rpo B and rpo C. Because this claim 1 limitation is neither described or suggested by Goh, Applicants request withdrawal of the rejection.

The anticipation rejection of Claims 1-3 and 5 as being unpatentable over Planet is respectfully traversed. The cancellation of Claim 5 obviates the rejection for this claim. In the detection method of Planet, the non-coding intergenic sequence between the genes rpoB and rpoC is not amplified. More precisely, the primers used for amplification in Planet are located in 5' of the coding sequence of gene rplA dn in 3' in the sequence of gene rpoB (Please see Figure 1 of Planet). Planet therefore amplifies a target sequence in the operon rplKAJL-rpoBC, which is different from the target sequence amplified in Claim 1. Thus, Planet does not describe or suggest a key limitation of Claim 1. Withdrawal of the rejection is requsted.

The anticipation rejection of Claims 1-3 and 5 as being unpatentable over Dennis is respectfully traversed. The rejection of Claim 5 is obviated by cancellation of this claim. Dennis relates to the preparation and analysis of deletion mutants in the intergenic region between genes rp1L and rpoB. Dennis does not describe or suggest amplifying a non-coding intergenic region between genes rpoB and rpoC, which is described in present Claim 1. Further, Dennis does not describe or suggest an identification step (another limitation of present Claim 1) but rather only the preparation of deletion mutants and the analysis of the impact of mutations on the transcription of gene rpoB. Accordingly, the presently claimed method is not described or suggested by Dennis. Withdrawal of the rejection is respectfully requested.

Applicants submit the present application is now in condition for allowance. Early notification to this effect is earnestly solicited.

Respectfully submitted,

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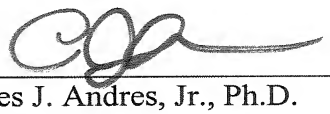
MAIER & NEUSTADT, P.C.
Norman F. Oblon



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# Normal Flora

*Charles Patrick Davis*

## General Concepts

### Significance of the Normal Flora

The normal flora influences the anatomy, physiology, susceptibility to pathogens, and morbidity of the host.

### Skin Flora

The varied environment of the skin results in locally dense or sparse populations, with Gram-positive organisms (e.g., staphylococci, micrococci, diphtheroids) usually predominating.

### Oral and Upper Respiratory Tract Flora

A varied microbial flora is found in the oral cavity, and streptococcal anaerobes inhabit the gingival crevice. The pharynx can be a point of entry and initial colonization for Neisseria, Bordetella, Corynebacterium, and Streptococcus spp.

### Gastrointestinal Tract Flora

Organisms in the stomach are usually transient, and their populations are kept low ($10^3$ to $10^6$/g of contents) by acidity. Helicobacter pylori is a potential stomach pathogen that apparently plays a role in the formation of certain ulcer types. In normal hosts the duodenal flora is sparse (0 to $10^3$/g of contents). The ileum contains a moderately mixed flora ($10^6$ to $10^8$/g of contents). The flora of the large bowel is dense ($10^9$ to $10^{11}$/g of contents) and is composed predominantly of anaerobes. These organisms participate in bile acid conversion and in vitamin K and ammonia production in the large bowel. They can also cause intestinal abscesses and peritonitis.

### Urogenital Flora

The vaginal flora changes with the age of the individual, the vaginal pH, and hormone levels. Transient organisms (e.g., Candida spp) frequently cause vaginitis. The distal urethra contains a sparse mixed flora; these organisms are present in urine specimens ($10^4$/ml) unless a clean-catch, midstream specimen is obtained.

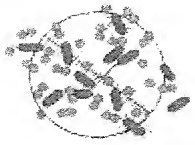
### Conjunctival Flora

The conjunctiva harbors few or no organisms. Haemophilus and Staphylococcus are among the genera most often detected.

### Host Infection

Many elements of the normal flora may act as opportunistic pathogens, especially in hosts rendered susceptible by rheumatic heart disease, immunosuppression, radiation therapy, chemotherapy,

perforated mucous membranes, etc. The flora of the gingival crevice causes dental caries in about 80 percent of the population.



# INTRODUCTION

A diverse microbial flora is associated with the skin and mucous membranes of every human being from shortly after birth until death. The human body, which contains about $10^{13}$ cells, routinely harbors about $10^{14}$ bacteria (Fig. 6-1). This bacterial population constitutes the normal microbial flora. The normal microbial flora is relatively stable, with specific genera populating various body regions during particular periods in an individual's life. Microorganisms of the normal flora may aid the host (by competing for microenvironments more effectively than such pathogens as Salmonella spp or by producing nutrients the host can use), may harm the host (by causing dental caries, abscesses, or other infectious diseases), or may exist as commensals (inhabiting the host for long periods without causing detectable harm or benefit). Even though most elements of the normal microbial flora inhabiting the human skin, nails, eyes, oropharynx, genitalia, and gastrointestinal tract are harmless in healthy individuals, these organisms frequently cause disease in compromised hosts. Viruses and parasites are not considered members of the normal microbial flora by most investigators because they are not commensals and do not aid the host.

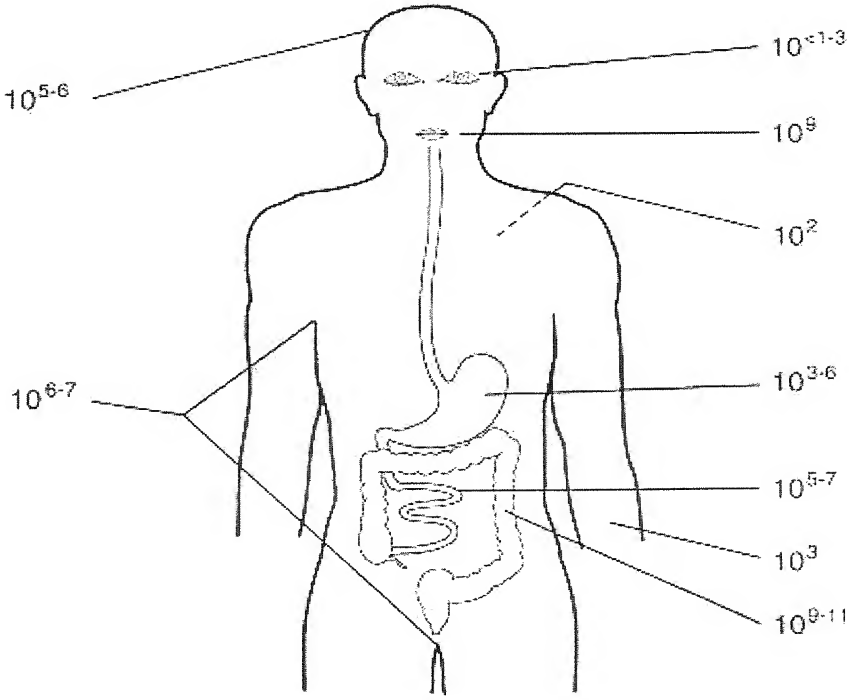



**FIGURE 6-1 Numbers of bacteria that colonize different parts of the body.** Numbers represent the number of organisms per gram of homogenized tissue or fluid or per square centimeter of skin surface.

## Significance of the Normal Flora

The fact that the normal flora substantially influences the well-being of the host was not well understood until germ-free animals became available. Germ-free animals were obtained by cesarean

section and maintained in special isolators; this allowed the investigator to raise them in an environment free from detectable viruses, bacteria, and other organisms. Two interesting observations were made about animals raised under germ-free conditions. First, the germ-free animals lived almost twice as long as their conventionally maintained counterparts, and second, the major causes of death were different in the two groups. Infection often caused death in conventional animals, but intestinal atonia frequently killed germ-free animals. Other investigations showed that germ-free animals have anatomic, physiologic, and immunologic features not shared with conventional animals. For example, in germ-free animals, the alimentary lamina propria is underdeveloped, little or no immunoglobulin is present in sera or secretions, intestinal motility is reduced, and the intestinal epithelial cell renewal rate is approximately one-half that of normal animals (4 rather than 2 days).

Although the foregoing indicates that bacterial flora may be undesirable, studies with antibiotic treated animals suggest that the flora protects individuals from pathogens. Investigators have used streptomycin to reduce the normal flora and have then infected animals with streptomycin-resistant Salmonella. Normally, about $10^6$ organisms are needed to establish a gastrointestinal infection, but in streptomycin-treated animals whose flora is altered, fewer than 10 organisms were needed to cause infectious disease. Further studies suggested that fermentation products (acetic and butyric acids) produced by the normal flora inhibited Salmonella growth in the gastrointestinal tract. Figure 6-2 shows some of the factors that are important in the competition between the normal flora and bacterial pathogens.

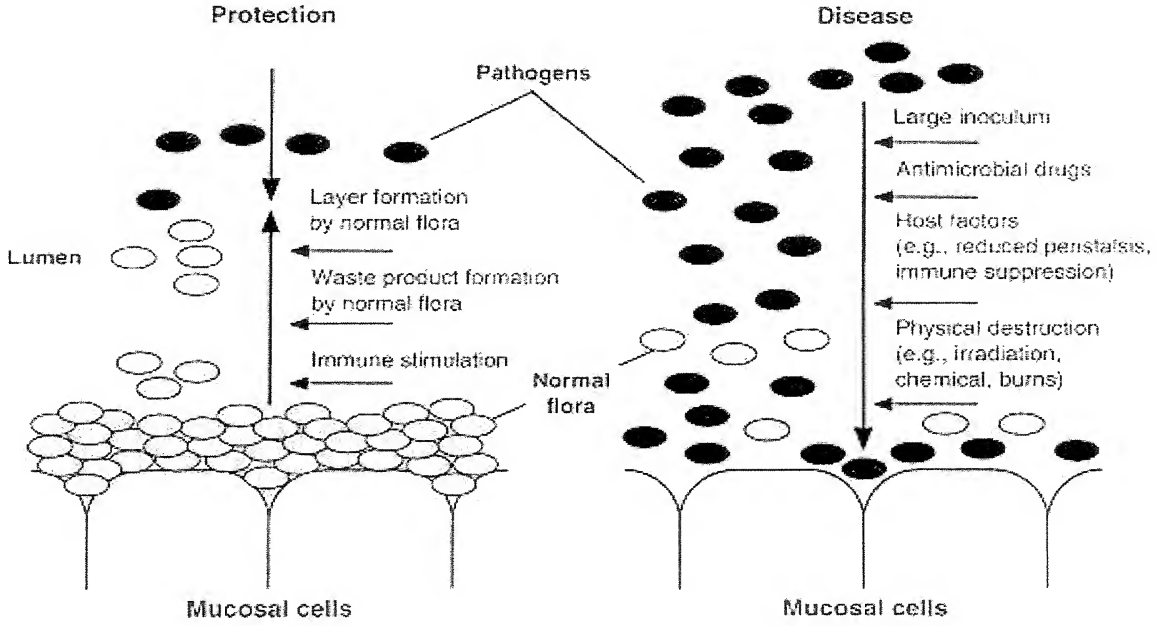



**FIGURE 6-2 Mechanisms by which the normal flora competes with invading pathogens.** Compare this schematic with Figure 6-3.

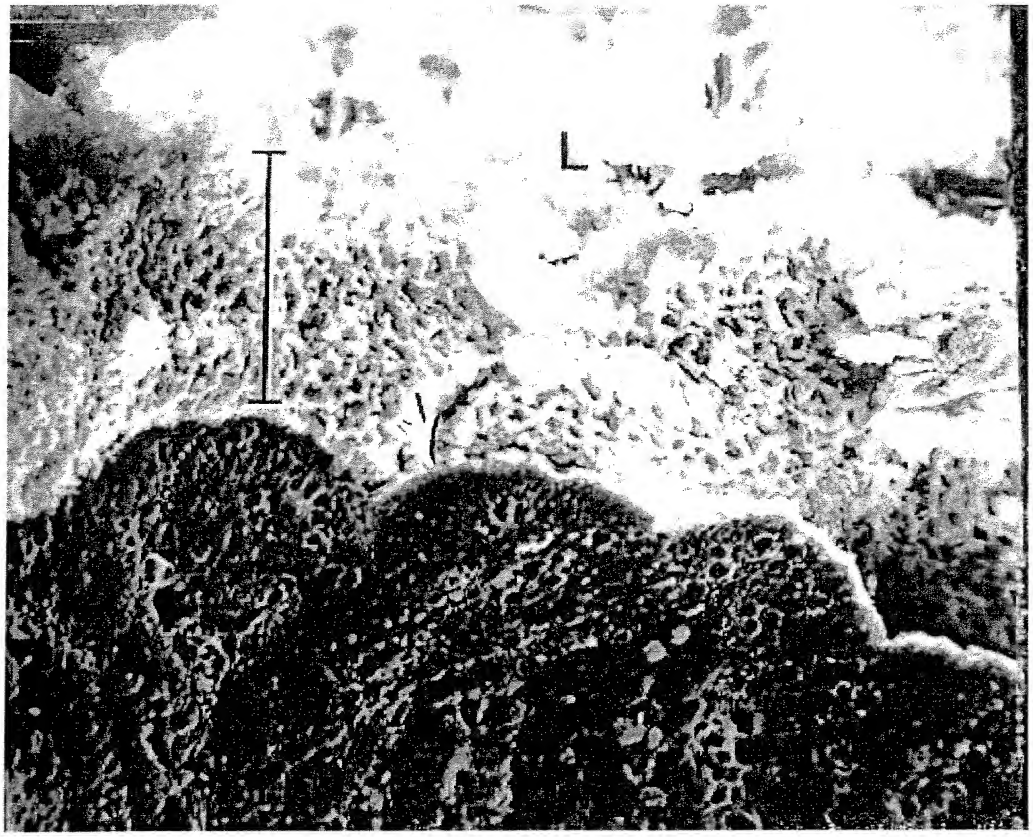



**FIGURE 6-3 (A) Scanning electron micrograph of a cross-section of rat colonic mucosa.** The bar indicates the thick layer of bacteria between the mucosal surface and the lumen (L) (X 262,)

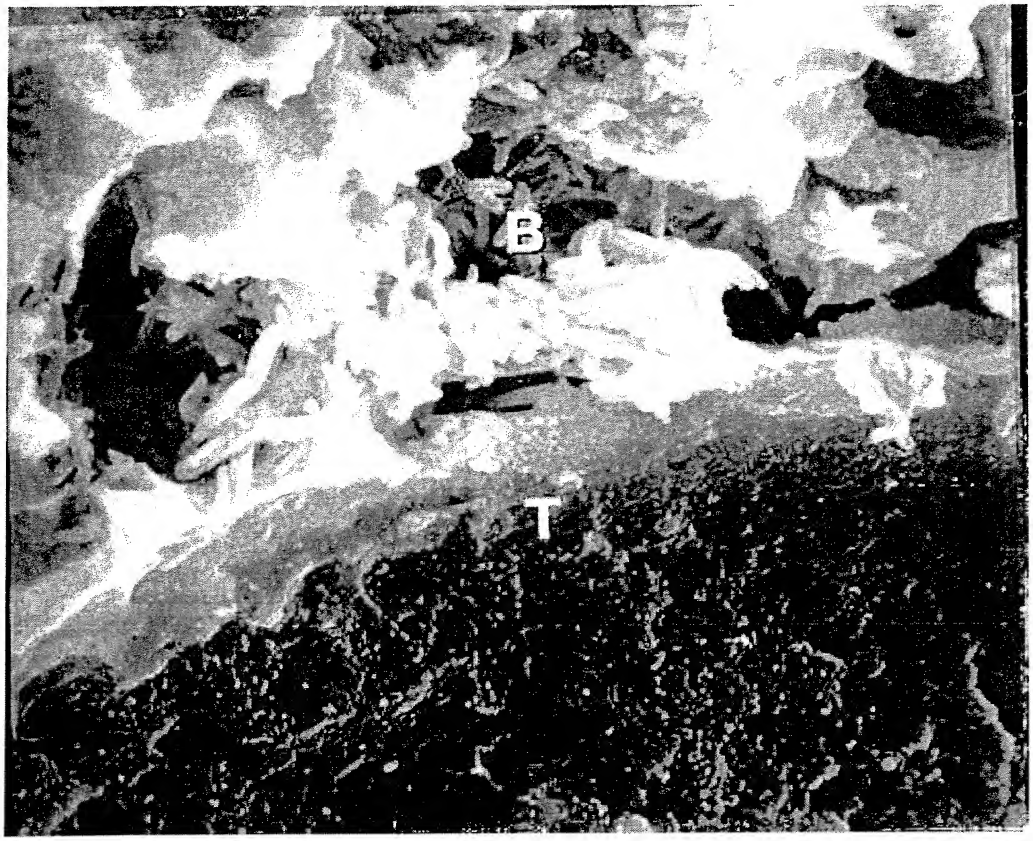



**FIGURE 6-3 (B) Higher magnification of the area indicated by the arrow in Fig. A,** showing a mass of bacteria (B) immediately adjacent to colonized intestinal tissue (T), (X2,624.) (Figure from Davis CP: Preservation of bacteria and their microenvironmental association in the rat by freezing.

Appl Environ Microbiol 31:310,1976, with permission.)

The normal flora in humans usually develops in an orderly sequence, or succession, after birth, leading to the stable populations of bacteria that make up the normal adult flora. The main factor determining the composition of the normal flora in a body region is the nature of the local environment, which is determined by pH, temperature, redox potential, and oxygen, water, and nutrient levels. Other factors such as peristalsis, saliva, lysozyme secretion, and secretion of immunoglobulins also play roles in flora control. The local environment is like a concerto in which one principal instrument usually dominates. For example, an infant begins to contact organisms as it moves through the birth canal. A Gram-positive population (bifidobacteria arid lactobacilli) predominates in the gastrointestinal tract early in life if the infant is breast-fed. This bacterial population is reduced and displaced somewhat by a Gram-negative flora (Enterobacteriaceae) when the baby is bottle-fed. The type of liquid diet provided to the infant is the principal instrument of this flora control; immunoglobulins and, perhaps, other elements in breast milk may also be important.

What, then, is the significance of the normal flora? Animal and some human studies suggest that the flora influences human anatomy, physiology, lifespan, and, ultimately, cause of death. Although the causal relationship of flora to death and disease in humans is accepted, of her roles of the human microflora need further study.

## Normal Flora of Skin

Skin provides good examples of various microenvironments. Skin regions have been compared to geographic regions of Earth: the desert of the forearm, the cool woods of the scalp, and the tropical forest of the armpit. The composition of the dermal microflora varies from site to site according to the character of the microenvironment. A different bacterial flora characterizes each of three regions of skin: (1) axilla, perineum, and toe webs; (2) hand, face and trunk; and (3) upper arms and legs. Skin sites with partial occlusion (axilla, perineum, and toe webs) harbor more microorganisms than do less occluded areas (legs, arms, and trunk). These quantitative differences may relate to increased amount of moisture, higher body temperature, and greater concentrations of skin surface lipids. The axilla, perineum, and toe webs are more frequently colonized by Gram-negative bacilli than are drier areas of the skin.

The number of bacteria on an individual's skin remains relatively constant; bacterial survival and the extent of colonization probably depend partly on the exposure of skin to a particular environment and partly on the innate and species-specific bactericidal activity in skin. Also, a high degree of specificity is involved in the adherence of bacteria to epithelial surfaces. Not all bacteria attach to skin; staphylococci, which are the major element of the nasal flora, possess a distinct advantage over viridans streptococci in colonizing the nasal mucosa. Conversely, viridans streptococci are not seen in large numbers on the skin or in the nose but dominate the oral flora.

The microbiology literature is inconsistent about the density of bacteria on the skin; one reason for this is the variety of methods used to collect skin bacteria. The scrub method yields the highest and most accurate counts for a given skin area. Most microorganisms live in the superficial layers of the stratum corneum and in the upper parts of the hair follicles. Some bacteria, however, reside in the deeper areas of the hair follicles and are beyond the reach of ordinary disinfection procedures. These bacteria are a reservoir for recolonization after the surface bacteria are removed.

### Staphylococcus epidermidis

S epidermidis is a major inhabitant of the skin, and in some areas it makes up more than 90 percent of the resident aerobic flora.

### Staphylococcus aureus

The nose and perineum are the most common sites for S aureus colonization, which is present in 10 percent to more than 40 percent of normal adults. S aureus is prevalent (67 percent) on vulvar skin.

Its occurrence in the nasal passages varies with age, being greater in the newborn, less in adults. S aureus is extremely common (80 to 100 percent) on the skin of patients with certain dermatologic diseases such as atopic dermatitis, but the reason for this finding is unclear.

## Micrococci

Micrococci are not as common as staphylococci and diphtheroids; however, they are frequently present on normal skin. Micrococcus luteus, the predominant species, usually accounts for 20 to 80 percent of the micrococci isolated from the skin.

## Diphtheroids (Coryneforms)

The term diphtheroid denotes a wide range of bacteria belonging to the genus Corynebacterium. Classification of diphtheroids remains unsatisfactory; for convenience, cutaneous diphtheroids have been categorized into the following four groups: lipophilic or nonlipophilic diphtheroids; anaerobic diphtheroids; diphtheroids producing porphyrins (coral red fluorescence when viewed under ultraviolet light); and those that possess some keratinolytic enzymes and are associated with trichomycosis axillaris (infection of axillary hair). Lipophilic diphtheroids are extremely common in the axilla, whereas nonlipophilic strains are found more commonly on glabrous skin.

Anaerobic diphtheroids are most common in areas rich in sebaceous glands. Although the name Corynebacterium acnes was originally used to describe skin anaerobic diphtheroids, these are now classified as Propionibacterium acnes and as P granulosum. P acnes is seen eight times more frequently than P granulosum in acne lesions and is probably involved in acne pathogenesis. Children younger than 10 years are rarely colonized with P acnes. The appearance of this organism on the skin is probably related to the onset of secretion of sebum (a semi-fluid substance composed of fatty acids and epithelial debris secreted from sebaceous glands) at puberty. P avidum, the third species of cutaneous anaerobic diphtheroids, is rare in acne lesions and is more often isolated from the axilla.

## Streptococci

Streptococci, especially ß-hemolytic streptococci, are rarely seen on normal skin. The paucity of ß-hemolytic streptococci on the skin is attributed at least in part to the presence of lipids on the skin, as these lipids are lethal to streptococci. Other groups of streptococci, such as a-hemolytic streptococci, exist primarily in the mouth, from where they may, in rare instances, spread to the skin.

## Gram-Negative Bacilli

Gram-negative bacteria make up a small proportion of the skin flora. In view of their extraordinary numbers in the gut and in the natural environment, their scarcity on skin is striking. They are seen in moist intertriginous areas, such as the toe webs and axilla, and not on dry skin. Desiccation is the major factor preventing the multiplication of Gram-negative bacteria on intact skin. Enterobacter, Klebsiella, Escherichia coli, and Proteus spp are the predominant Gram-negative organisms found on the skin. Acinetobacter spp also occurs on the skin of normal individuals and, like other Gram-negative bacteria, is more common in the moist intertriginous areas.

## Nail Flora

The microbiology of a normal nail is generally similar to that of the skin. Dust particles and other extraneous materials may get trapped under the nail, depending on what the nail contacts. In addition to resident skin flora, these dust particles may carry fungi and bacilli. Aspergillus, Penicillium, Cladosporium, and Mucor are the major types of fungi found under the nails.

## Oral and Upper Respiratory Tract Flora

The oral flora is involved in dental caries and periodontal disease, which affect about 80 percent. of the population in the Western world. The oral flora, its interactions with the host, and its response to environmental factors are thoroughly discussed in another Chapter. Anaerobes in the oral flora are responsible for many of the brain, face, and lung infections that are frequently manifested by abscess formation.

The pharynx and trachea contain primarily those bacterial genera found in the normal oral cavity (for example, alpha-and ß-hemolytic streptococci); however, anaerobes, staphylococci, neisseriae, diphtheroids, and others are also present. Potentially pathogenic organisms such as Haemophilus, mycoplasmas, and pneumococci may also be found in the pharynx. Anaerobic organisms also are reported frequently. The upper respiratory tract is so often the site of initial colonization by pathogens (Neisseria meningitides, C diphtheriae, Bordetella pertussis, and many others) and could be considered the first region of attack for such organisms. In contrast, the lower respiratory tract (small bronchi and alveoli) is usually sterile, because particles the size of bacteria do not readily reach it. If bacteria do reach these regions, they encounter host defense mechanisms, such as alveolar macrophages, that are not present in the pharynx.

## Gastrointestinal Tract Flora

The stomach is a relatively hostile environment for bacteria. It contains bacteria swallowed with the food and those dislodged from the mouth. Acidity lowers the bacterial count, which is highest (approximately $10^3$ to $10^6$ organisms/g of contents) after meals and lowest (frequently undetectable) after digestion. Some Helicobacter species can colonize the stomach and are associated with type B gastritis and peptic ulcer disease. Aspirates of duodenal or jejunal fluid contain approximately $10^3$ organisms/ml in most individuals. Most of the bacteria cultured (streptococci, lactobacilli, Bacteroides) are thought to be transients. Levels of $10^5$ to about $10^7$ bacteria/ml in such aspirates usually indicate an abnormality in the digestive system (for example, achlorhydria or malabsorption syndrome). Rapid peristalsis and the presence of bile may explain in part the paucity of organisms in the upper gastrointestinal tract. Further along the jejunum and into the ileum, bacterial populations begin to increase, and at the ileocecal junction they reach levels of $10^6$ to $10^8$ organisms/ml, with streptococci, lactobacilli, Bacteroides, and bifidobacteria predominating.

Concentrations of $10^9$ to $10^{11}$ bacteria/g of contents are frequently found in human colon and feces. This flora includes a bewildering array of bacteria (more than 400 species have been identified); nonetheless, 95 to 99 percent belong to anaerobic genera such as Bacteroides, Bifidobacterium, Eubacterium, Peptostreptococcus, and Clostridium. In this highly anaerobic region of the intestine, these genera proliferate, occupy most available niches, and produce metabolic waste products such as acetic, butyric, and lactic acids. The strict anaerobic conditions, physical exclusion (as is shown in many animal studies), and bacterial waste products are factors that inhibit the growth of other bacteria in the large bowel.

Although the normal flora can inhibit pathogens, many of its members can produce disease in humans. Anaerobes in the intestinal tract are the primary agents of intra-abdominal abscesses and peritonitis. Bowel perforations produced by appendicitis, cancer, infarction, surgery, or gunshot wounds almost always seed the peritoneal cavity and adjacent organs with the normal flora. Anaerobes can also cause problems within the gastrointestinal lumen. Treatment with antibiotics may allow certain anaerobic species to become predominant and cause disease. For example, *Clostridium difficile,* which can remain viable in a patient undergoing antimicrobial therapy, may produce pseudomembranous colitis. Other intestinal pathologic conditions or surgery can cause bacterial overgrowth in the upper small intestine. Anaerobic bacteria can then deconjugate bile acids in this region and bind available vitamin B12 so that the vitamin and fats are malabsorbed. In these situations, the patient usually has been compromised in some way; therefore, the infection caused by the normal intestinal flora is secondary to another problem.

More information is available on the animal than the human microflora. Research on animals has revealed that unusual filamentous microorganisms attach to ileal epithelial cells and modify host

membranes with few or no harmful effects. Microorganisms have been observed in thick layers on gastrointestinal surfaces (Fig. 6-3) and in the crypts of Lieberkuhn. Other studies indicate that the immune response can be modulated by the intestinal flora. Studies of the role of the intestinal flora in biosynthesis of vitamin K and other host-utilizable products, conversion of bile acids (perhaps to cocarcinogens), and ammonia production (which can play a role in hepatic coma) show the dual role of the microbial flora in influencing the health of the host. More basic studies of the human bowel flora are necessary to define their effect on humans.

## Urogenital Flora

The type of bacterial flora found in the vagina depends on the age, pH, and hormonal levels of the host. Lactobacillus spp predominate in female infants (vaginal pH, approximately 5) during the first month of life. Glycogen secretion seems to cease from about I month of age to puberty. During this time, diphtheroids, *S epidermidis*, streptococci, and *E coli* predominate at a higher pH (approximately pH 7). At puberty, glycogen secretion resumes, the pH drops, and women acquire an adult flora in which L acidophilus, corynebacteria, peptostreptococci, staphylococci, streptococci, and Bacteroides predominate. After menopause, pH again rises, less glycogen is secreted, and the flora returns to that found in prepubescent females. Yeasts (Torulopsis and Candida) are occasionally found in the vagina (10 to 30 percent of women); these sometimes increase and cause vaginitis.

In the anterior urethra of humans, *S epidermidis,* enterococci, and diphtheroids are found frequently; *E coli*, Proteus, and Neisseria (nonpathogenic species) are reported occasionally (10 to 30 percent). Because of the normal flora residing in the urethra, care must be taken in clinically interpreting urine cultures; urine samples may contain these organisms at a level of $10^4$/ml if a midstream (clean-catch) specimen is not obtained.

## Conjunctival Flora

The conjunctival flora is sparse. Approximately 17 to 49 percent of culture samples are negative. Lysozyme, secreted in tears, may play a role in controlling the bacteria by interfering with their cell wall formation. When positive samples show bacteria, corynebacteria, neisseriae, and moraxellae are cultured. Staphylococci and streptococci are also present, and recent reports indicate that Haemophilus parainfluenzae is present in 25 percent of conjunctival samples.

## Host Infection by Elements of the Normal Flora

This chapter has briefly described the normal human flora; however, the pathogenic mechanisms of various genera or the clinical syndromes in which they are involved was not discussed. Although such material is presented in other chapters, note that a breach in mucosal surfaces often results in infection of the host by members of the normal flora. Caries, periodontal disease, abscesses, foul-smelling discharges, and endocarditis are hallmarks of infections with members of the normal human flora (Fig. 6-4). In addition, impairment of the host (for example, those with heart failure or leukemia) or host defenses (due to immunosuppression, chemotherapy, or irradiation) may result in failure of the normal flora to suppress transient pathogens or may cause members of the normal flora to invade the host themselves. In either situation, the host may die.

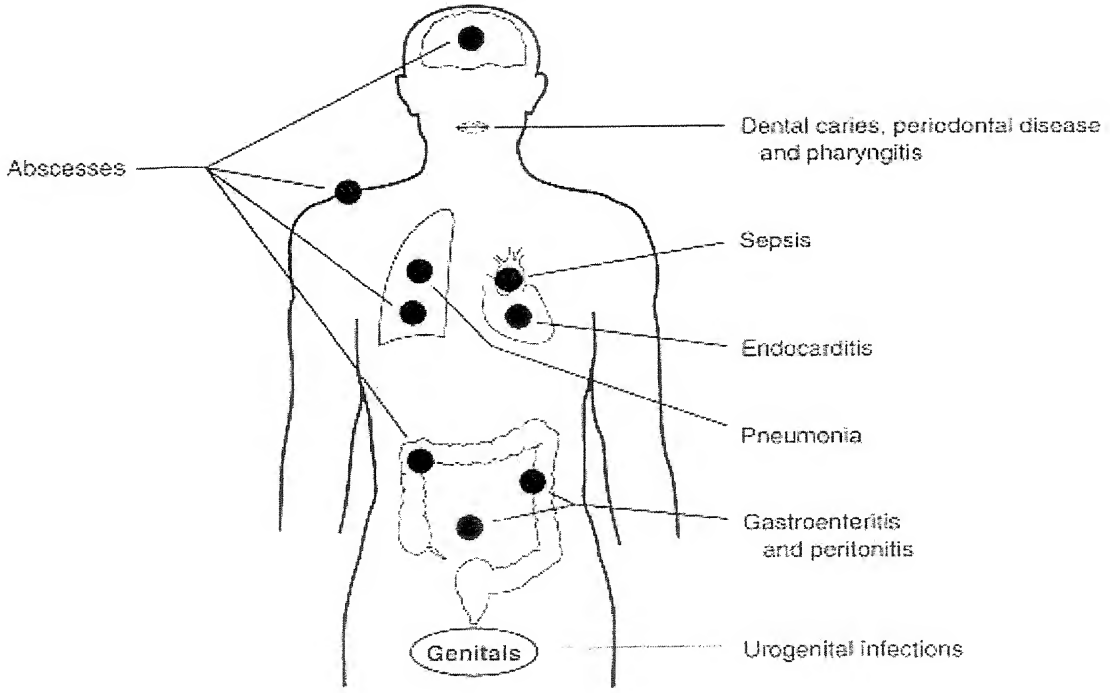



**FIGURE 6-4 Clinical conditions that may be caused by members of the normal flora.**

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